CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

TRANEXAMIC ACID COMPARED WITH HIGH-DOSE APROTININ IN PRIMARY ELECTIVE HEART OPERATIONS: EFFECTS ON PERIOPERATIVE BLEEDING AND ALLOGENEIC TRANSFUSIONS

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Objective: Since excessive fibrinolysis during cardiac surgery is frequently associated with abnormal perioperative bleeding, many authors have advocated prophylactic use of antifibrinolytic drugs to prevent hemorrhagic disorders. We compared the effects of tranexamic acid (a synthetic antifibrinolytic drug) with aprotinin (a natural derivative product with antifibrinolytic properties) on perioperative bleeding and the need for allogeneic transfusions.

Methods: In a single-center prospective randomized unblinded trial, 1040 consecutive patients undergoing primary, elective cardiac operations with cardiopulmonary bypass received either high-dose aprotinin or tranexamic acid. The aprotinin group (518 patients) received 280 mg in 20 minutes before the skin incision, 280 mg in the priming solution of the extracorporeal circuit, and a continuous infusion of 70 mg/h throughout the operation. The tranexamic acid group (522 patients) received 1 g in 20 minutes before the skin incision, 500 mg in the priming solution of the extracorporeal circuit, and a continuous infusion of 400 mg/h during the operation. Postoperative bleeding, perioperative transfusions, and hematologic variables were evaluated at fixed times. Postoperative thrombotic complications, intubation time, intensive care unit stay, and hospital stay were recorded.

Results: Postoperative bleeding was similar in the 2 groups: aprotinin 250 mL (150-400 mL) versus tranexamic acid 300 mL (200-450 mL) (median and 25th-75th quartiles), median difference of 50 mL (95% confidence intervals, 0-50 mL). The number of transfusions and the outcome did not differ.

Conclusions: Tranexamic acid and aprotinin show similar clinical effects on bleeding and allogeneic transfusion in patients undergoing primary elective heart operations. Since tranexamic acid is about 100 times cheaper than aprotinin, its use is preferable in this type of patient. (J Thorac Cardiovasc Surg 2000;120:520-7)

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Perioperative hemorrhagic syndromes frequently complicate the outcome of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[1] The interaction between the blood and foreign surfaces of the extracorporeal circuit induces platelet dysfunction and increased fibrinolytic activity, identified in previous studies as the most important factors of postoperative hemostatic derangement.[2] The exposure to allogeneic blood-derived products is related to the risk of nonhemolytic transfusional and anaphylactic reactions, as well as to infectious diseases such as acquired immunodeficiency syndrome and viral hepatitis.[3] Procedures

Table I. *Baseline characteristics*

	Aprotinin group (N = 518)	*Tranexamic acid group (N = 522)*	P*
Age, y	62 ± 10	61 ± 10	.1
Sex, No. (%)	412 (79.5)	415 (79.5)	.9
Height, cm	168 ± 11	169 ± 10	.3
Weight, kg	73 ± 12	72 ± 12	.3
Baseline ejection fraction, %	60 ± 9	59 ± 10	.1
Patients with baseline ejection fraction < 35%, No. (%)	41 (7.9)	39 (7.5)	.7
Coexisting illness, No. (%)			
Hypertension	153 (29.5)	162 (31)	.6
Diabetes	76 (14.7)	78 (14.9)	.9
Peripheral vascular disease	29 (5.6)	31 (5.9)	.8
Preoperative aspirin, No. (%)	92 (17.8)	98 (18.8)	.7
Preoperative heparin, No. (%)	88 (17)	87 (16.7)	.9

*The *t* test or χ^2 test was used as appropriate; no significant differences were noted between groups. Plus-minus values are means ± standard deviation.

such as autologous blood predonation, intraoperative isovolumic hemodilution, and equipment for blood cell processing were introduced in cardiac surgery to reduce the need for allogeneic transfusions.[4] More recently, the hemostatic effects of drugs such as aprotinin, tranexamic acid, ε-aminocaproic acid, desmopressin, and dipyridamole have been studied. Whereas the efficacy of desmopressin and dipyridamole could not be demonstrated, aprotinin, a natural antiprotease with antifibrinolytic properties, and ε-aminocaproic acid and tranexamic acid, 2 synthetic antifibrinolytic drugs, allowed a significant reduction of perioperative bleeding and of the need for allogeneic transfusions.[5] The disadvantages of aprotinin are the high cost and the risk of anaphylactic reactions.[6] To overcome these limits, we decided to compare the hemostatic effects of aprotinin with those of tranexamic acid, a synthetic, low-cost antifibrinolytic drug 10 times more potent than ε-aminocaproic acid, in a large series of adult patients undergoing primary elective cardiac surgery. The amount of the bleeding at various times was considered to be the main end point of the study; the entity of allogeneic blood-derived products transfused, postoperative thrombotic complications, and outcome were also considered.

Methods

Patient population and eligibility criteria. After obtaining institutional review board and informed consent, from June 1, 1996, to July 30, 1997, we conducted an unblinded prospective study in 1040 consecutive adult patients (age > 18 years) scheduled for primary elective cardiac surgery necessitating CPB in our institution. Exclusion criteria were impaired renal function (serum creatinine level > 2 mg/dL), advanced hepatic dysfunction (active chronic hepatitis or cirrhosis), and hematologic diseases. Preoperative treatment with aspirin or heparin was not a contraindication to enrollment in the study.

Treatment groups and operative procedures. By means of a computer-generated random number sequence, 518 patients were randomly allocated to receive aprotinin, 280 mg for 20 minutes before the surgical incision, followed by a constant infusion of 70 mg/h until the end of the operation, while 280 mg was added to the priming solution of the CPB circuit; 522 patients were randomized to receive tranexamic acid, 1 g over 20 minutes before the surgical incision, followed by a constant infusion of 400 mg/h during the entire operative period, while 500 mg was added to the priming solution of the CPB circuit.

The anesthetic technique was standardized: each patient was premedicated with intramuscular scopolamine (0.5 mg), intramuscular morphine (0.1 mg/kg), and oral diazepam (0.1 mg/kg). Anesthesia was induced with fentanyl (0.02 mg/kg) and propofol (2 mg/kg) or midazolam (0.15 mg/kg) in patients with reduced cardiac function, defined as left ventricular ejection fraction below 35%. Muscle relaxation was obtained with pancuronium bromide (0.1 mg/kg). Anesthesia was maintained with fentanyl (up to 0.05 mg/kg), an infusion of propofol (6-10 $mg \cdot kg^{-1} \cdot h^{-1}$) or midazolam (0.1-0.2 $mg \cdot kg^{-1} \cdot h^{-1}$) in patients with a reduced left ventricular ejection fraction, and isoflurane and pancuronium as needed. Patients with a reduced left ventricular ejection fraction and patients with preoperative compromised clinical conditions were monitored with a thermodilution catheter (Swan-Ganz; Baxter Healthcare Corp, Edwards Division, Santa Ana, Calif).

All patients were operated on through a median sternotomy. During coronary artery bypass grafting procedures, the left internal thoracic artery was routinely harvested through a conventional pleurotomy access. The right internal thoracic artery or the saphenous veins (or both) were also isolated when needed, according to the surgeon's preference. Before aortic cannulation, porcine mucous heparin (3 mg/kg) was injected, and further heparin was administered to maintain a kaolin-activated coagulation time above 480 seconds. A hollow-fiber membrane oxygenator was used, and the priming solution of

Table II. *Baseline hematologic data*

Variable	*Aprotinin group (N = 518)*	*Tranexamic acid group (N = 522)*	P*
Activated clotting time, s	152 [138-171]	151 [136-168]	.07
Hemoglobin, g/dL	13.8 ± 1.6	13.9 ± 1.5	.2
Hematocrit, %	39.9 ± 4.4	40.3 ± 4.0	.2
Platelet count, $10^3/mm^3$†	209 ± 55	210 ± 57	.9
Prothrombin time, INR	1.04 ± 0.21	1.03 ± 0.2	.4
aPTT, ratio	1.21 ± 0.46	1.18 ± 0.42	.3
Fibrinogen, mg/dL†	357 ± 67	332 ± 86	.3
D-dimer, μg/mL†	0.79 ± 0.7	0.7 ± 0.5	.2
Creatinine, mg/dL	0.9 [0.74-1.02]	0.88 [0.7-1.03]	.6
CK, U/L	68 [49-98]	67 [50-98]	.9

Blood samples for evaluation of plasmatic concentrations of fibrinogen and D-dimer obtained from 100 consecutive patients (50 patients for each group). *aPTT,* Activated thromboplastin time; *CK,* creatine kinase; *INR,* international normalized ratio.

*The *t* test or Mann-Whitney *U* test was used as appropriate; no significant differences were noted between groups. Plus-minus values are mean ± standard deviation. Non-normally distributed data are indicated as median and (in brackets) 25th to 75th percentiles.

†Log transformed: values are geometric means.

the circuit consisted of 1750 mL of a balanced crystalloid/colloid solution (Ringer lactate, 1350 mL; 18% mannitol, 250 mL; and plasma expander, 150 mL). Nonpulsatile blood flow was obtained with a roller pump (2.0-2.4 $L \cdot min^{-1} \cdot m^{-2}$). Blood temperature was kept between 32°C and 35°C. Myocardial protection during aortic crossclamping was achieved with the Buckberg method of blood cardioplegia. The total dose of heparin administered during CPB was reversed with protamine sulfate (ratio 1:1). Intraoperative cardiogenic shock refractory to maximal inotropic therapy and intra-aortic balloon pumping was treated by means of delayed sternal closure and, if needed, with a ventricular assist device. After termination of CPB, the remaining cellular content of the oxygenator and salvaged blood were concentrated with a cell separator and reinfused. Pericardial, mediastinal, and pleural drains were inserted before chest closure and continuous low-grade suction was instituted.

Postoperative evaluation. Postoperative blood loss through the drainage tubes was recorded during the first 24 hours and was not reinfused. Drains were removed when bleeding in the previous 4 hours was less than 100 mL. Plasma concentrations of hemoglobin, hematocrit, and platelets, prothrombin time, activated partial thromboplastin time (aPTT), creatinine, creatine kinase (CK), and creatine kinase myocardial band isoenzyme (CK-MB) were evaluated at the following times: after the induction of anesthesia (basal), at admission to the intensive care unit (ICU) (time 1), after 4 hours (time 2), and at 6 AM on the first and second postoperative days (time 3 and time 4). As markers of fibrinolysis, serologic values of fibrinogen and D-dimers were tested in a subgroup of 100 consecutive patients (50 patients for each group).

Transfusion protocol and criteria for surgical re-exploration for bleeding. Criteria for transfusion were standardized and indicated as units of packed red blood cells, fresh frozen plasma, and platelet concentrates. Criteria for transfusion of packed red blood cells were as follows: hematocrit value less than 18% and hemoglobin value less than 6 g/dL during CPB; hematocrit value less than 24% and hemoglobin value less than 8 g/dL accompanied by signs or symptoms of hypovolemia after CPB and during the ICU stay. The criterion for transfusion of fresh frozen plasma was a prothrombin time greater than 1.5 (international normalized ratio) with excessive bleeding, defined as greater than 200 mL/h for 2 consecutive hours. The criterion for transfusion of platelet concentrates was a platelet count less than $50{,}000/mm^3$ with excessive bleeding (>200 mL/h for 2 consecutive hours). Surgical re-exploration was performed if bleeding in the first 2 hours was greater than 300 mL/h or if greater than 200 mL/h for 4 consecutive hours with normal coagulation parameters. Bleeding of more than 600 mL in the first 24 hours was considered excessive postoperative bleeding. Cases of perioperative myocardial infarction (electrocardiographic new Q waves and CK-MB/CK ratio greater than 10%), postoperative renal failure (creatinine content 2 times the basal value or need for dialysis), thromboembolic complications, and major neurologic dysfunction (transient ischemic attack, ictus cerebri) were recorded. Intubation time, ICU stay, and hospital stay were also considered.

Statistical analysis. The main end point of the study was the amount of total bleeding. Sample size was calculated according to the formula for equivalence trial. The 2 treatments will be considered equivalent if the 95% 2-sided confidence interval for the treatment difference of total bleeding falls within the interval ± 50 mL, assuming a standard deviation of 200 mL. Five hundred subjects for each group are necessary to have a power of 0.95 to conclude that the 2 treatments are equivalent, if they are, in fact, identical. We used the Shapiro-Wilk statistic to test the normality of the distribution of continuous variables. When possible, log transformation was used to normalize distributions, and geometric means are presented. To compare baseline, operative, and postoperative variables, we used the *t* test or Mann-Whitney *U* test as appropriate. Continuous variables are presented as means ± standard deviation or as median and 25th to 75th quartiles as appropriate. The χ^2 test or Fisher exact test was used to compare categoric data. A 2-way mixed-design analysis of variance for repeated measures was used (PROC GLM; SAS Institute, Inc, Cary, NC) to investigate the effects of the time, of the treatment, and of the interaction time · treatment

Table III. *Operative data*

	Aprotinin group (N = 518)	*Tranexamic acid group (N = 522)*	P*
CABG, No. (%)	388 (74.9)	390 (74.7)	.9
Valvular surgery, No. (%)	62 (12)	70 (13.4)	.6
ASD repair, No. (%)	7 (1.4)	7 (1.4)	.99
Combined intervention, No. (%)	61 (11.8)	55 (10.5)	.6
Thermodilution catheter, No. (%)	89 (17.2)	89 (17.1)	.9
CPB time, min	121 [95-145]	117 [92-137]	.07
ACC time, min	83 [67-106]	81 [64-99]	.06
Closure time, min	60 [60-75]	60 [60-75]	.5
Distal anastomoses, no.	2.7 ± 0.9	2.9 ± 0.8	.001
Total heparin dose, mg	260 [210-300]	250 [210-300]	.5
Total protamine dose, mg	260 [210-300]	250 [210-300]	.6
Minimum hematocrit during CPB, %	23 [21-27]	23 [20-26]	.06
Minimum temperature during CPB, °C	32.2 ± 0.9	32.4 ± 1.1	.002
Intraoperative surgical complications requiring allogeneic transfusions, No. (%)	3 (0.6)	3 (0.6)	.99
IABP, No. (%)	22 (4.2)	24 (4.6)	.8
Delayed sternal closure for weaning from CPB, no. (%)	2 (0.4)	1 (0.2)	.7
VAD for weaning from CPB, No. (%)	3 (0.6)	3 (0.6)	.99

ACC, Aortic crossclamping; *ASD*, atrial septal defect; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass; *IABP*, intra-aortic balloon pump; *VAD*, ventricular assist device. Closure time is considered from the end of administration of protamine until the end of the surgical procedures.
*The $\chi 2$ test, Fisher exact test, or Mann-Whitney *U* test was used as appropriate; significant differences for $P < .01$. Plus-minus values are mean ± standard deviation. Non-normally distributed data are indicated as median and (in brackets) 25th to 75th percentiles.

on the coagulation data. The median differences of the bleeding between groups at different considered times are presented. As in equivalence trials, the confidence intervals are more informative than the conventional significance test. Confidence intervals of the median difference are also presented to evaluate the range for the possible true difference between the treatments. As many comparisons were performed between the 2 groups, only a highly statistically significant *P* value (<.01) was considered to reject the null hypothesis of no differences between groups. Data were analyzed with SAS statistical software.

Results

Following the "intention to treat" rule, all 1040 patients enrolled in the study were included in the statistical analysis, and their baseline characteristics and hematologic data are indicated in Tables I and II. There were no differences for each considered variable between the groups. Thirty-five patients (aprotinin group, n = 17; tranexamic acid group, n = 18) who differed from the main body of patients were included in the analysis (see appendix). Table III shows operative data. Statistically significant differences were found in terms of the number of distal anastomoses performed in patients undergoing myocardial revascularization and in terms of minimum temperature recorded during CPB. The 2 groups had the same number of patients requiring delayed sternal closure or a ventricular assist device for weaning from CPB. Table IV shows significant differences found among postoperative hematologic and coagulation data. Particularly in the aprotinin group, the hematocrit and hemoglobin values were higher ($P < .001$) and the aPTT was longer ($P < .001$) at each given time. All the coagulation values changed with time ($P < .001$). The time · treatment effect difference was statistically significant for hemoglobin, hematocrit, and aPTT ($P < .001$). Plasma levels of fibrinogen and D-dimers, which were evaluated in a subgroup of 100 subjects, did not change with time (fibrinogen, $P = .06$; D-dimer, $P = .3$) and were not different in the 2 groups (fibrinogen, $P = .7$; D-dimer, $P = .3$). Postoperative bleeding at various considered times is presented in Table V. The median differences of bleeding between groups ranged from 0 mL in the first 4 hours to 50 mL for total bleeding, and the 95% confidence intervals did not exceed 50 mL. As shown in Table VI, the amount of allogeneic blood-derived products transfused did not differ. Outcome data are displayed in Table VII. Three patients in each group required surgical re-exploration for excessive bleeding without evidence of a surgical bleeding site; 5 patients of the aprotinin group and 7 patients of the tranexamic acid group had a surgical source for bleeding at re-exploration. The same number of patients in the 2 groups had excessive bleeding (>600 mL in the first 24 hours). The prevalence of postoperative complications did not differ between the 2 groups. Finally, intubation time, ICU and hospital stay, and the mortality in the 2 groups were similar.

Table IV. *Postoperative coagulation data*

	Treatment	*Baseline*	*Time 1*	*Time 2*	*Time 3*	*Time 4*
Hemoglobin	Aprotinin	13.8 ± 1.6	11.5 ± 1.7	11.5 ± 1.6	11.1 ± 1.4	10.7 ± 1.3
	Tranexamic acid	13.9 ± 1.5	11.2 ± 1.5	11.1 ± 1.5	10.9 ± 1.4	10.3 ± 1.2
Hematocrit	Aprotinin	39.9 ± 4.4	33.9 ± 4.8	33.9 ± 4.6	32.7 ± 4.1	31.4 ± 3.9
	Tranexamic acid	40.3 ± 4.0	32.9 ± 4.6	32.8 ± 4.6	31.7 ± 4.0	30.2 ± 3.7
PLT count[†]	Aprotinin	209 ± 55	132 ± 42	140 ± 42	136 ± 45	126 ± 43
	Tranexamic acid	210 ± 57	130 ± 42	137 ± 48	135 ± 45	129 ± 43
Pt	Aprotinin	1.04 ± 0.21	1.24 ± 0.17	1.18 ± 0.14	1.15 ± 0.11	1.1 ± 0.13
	Tranexamic acid	1.03 ± 0.2	1.23 ± 0.21	1.17 ± 0.12	1.14 ± 0.14	1.1 ± 0.17
aPTT	Aprotinin	1.21 ± 0.46	1.65 ± 0.38	1.44 ± 0.33	1.35 ± 0.23	1.29 ± 0.25
	Tranexamic acid	1.18 ± 0.42	1.26 ± 0.22	1.19 ± 0.21	1.2 ± 0.17	1.22 ± 0.23

aPTT, Activated thromboplastin time; *df,* degrees of freedom; *PLT,* platelet count; *Pt,* prothrombin time.
[*]Two-way mixed-model analysis of variance for repeated measures.
[†]Log-transformed: values are geometric mean ± standard deviations.

Table V. *Postoperative bleeding*

	Aprotinin (N = 518)	*Tranexamic acid (N = 522)*	*Difference between groups*
	Median [25th-75th percentiles]	*Median [25th-75th percentiles]*	*Median [95% CI of median]*
Bleeding 0-4 hours, mL	100 [50-200]	150 [100-200]	0 [0-50]
Bleeding 4-24 hours, mL	150 [100-200]	150 [100-200]	0 [0-0]
Total bleeding, mL	250 [150-400]	300 [200-450]	50 [0-50]

CI, Confidence interval.

Discussion

This is the largest single-center prospective randomized trial comparing the hemostatic effects of aprotinin and tranexamic acid in patients undergoing cardiac surgery with CPB. Perioperative hemorrhagic disorders due to extracorporeal circulation are a frequent complication in cardiac surgery: excessive postoperative bleeding increases the need for allogeneic blood-derived products, with the consequent risk of transfusion-related complications, and requires surgical re-exploration in about 2% to 6% of patients, with an increased rate of morbidity and mortality.[1] Different factors are implicated in coagulation disorders: surgical causes, heparin rebound, complement activation, hyperfibrinolysis, and platelet dysfunction. Previous studies demonstrated that platelet dysfunction and excessive fibrinolysis are the most frequently involved nonsurgical causes: the contact of the blood with the surfaces of the extracorporeal circuit induces the activation of the coagulation pathways, of fibrinolysis, and of platelets, with their aggregation mediated by the receptors glycoprotein IIb-IIIa and their degranulation.[7] The increase of fibrinolytic activity is due to the increased release of tissue-plasminogen activator from vascular endothelium, which starts during skin incision and continues during sternotomy and surgical tissue manipulation. This causes a rapid rise in plasma concentration during the first minutes of CPB, followed by the transformation of plasminogen into plasmin and the production of fibrin degradation products. At the same time, platelet aggregation is induced by the increased levels of thrombin and mediated by the fibrinogen and fibrinogen receptors glycoprotein IIb-IIIa, with secretion of α-granules and microparticle production. The result of these processes is frequently an altered perioperative hemostasis.[8]

Drugs like aprotinin and tranexamic acid were introduced in cardiac surgery to block the formation of plasmin, preserve platelet function, and reduce perioperative hemorrhagic disorders and the consequent increased need for allogeneic transfusions. Aprotinin is a natural derivative product obtained from bovine lung with an inhibitory effect on a wide series of serine proteases such as plasmin, kallikrein, and trypsin. The inhibition of plasmin produces the antifibrinolytic effects; the inactivation of kallikrein inhibits the contact activation system with inhibition of intrinsic coagulation pathway and the production of fibrin.[9] Platelet function defect during CPB is due to the decrease of both platelet surface glycoprotein Ib receptors (adhesive receptor for von Willebrand factor) and glycoprotein IIb-IIIa receptors (aggregation receptor for fibrinogen). Aprotinin provides a platelet protective effect with the preservation of both these receptors.[10] A high-dose aprotinin regimen is presently indicated as the

Treatment effect *F(df)*	P*	*Time effect* *F(df)*	P*	*Treatment* F(df)*	*Time interaction* P*
$7.7_{(1,771)}$	.006	$55.8_{(4,768)}$	<.001	$6.78_{(4,768)}$	<.001
$9.7_{(1,773)}$	.002	$72.1_{(4,770)}$	<.001	$6.07_{(4,770)}$	<.001
$.001_{(1,769)}$	.96	$74.6_{(4,766)}$	<.001	$1.76_{(4,766)}$	.1
$1.1_{(1,796)}$	.3	$19.4_{(4,793)}$	<.001	$0.16_{(4,793)}$	.9
$143_{(1,795)}$	<.001	$84.4_{(4,794)}$	<.001	$38.1_{(4,792)}$	<.001

Table VI. *Perioperative allogeneic transfusions*

	Aprotinin group (N = 518)	*Tranexamic acid group (N = 522)*	P*
PRBC in OR, units (patients transfused)	238 (106)	219 (100)	.6
PRBC 0-4 hours, units (patients transfused)	252 (108)	234 (100)	.5
Total PRBC, units (patients transfused)	543 (185)	504 (178)	.5
FFP in OR, units (patients transfused)	38 (9)	41 (8)	.8
FFP 0-4 hours, units (patients transfused)	110 (25)	116 (25)	.99
Total FFP, units (patients transfused)	169 (27)	181 (30)	.7
PLTC in OR, units (patients transfused)	16 (2)	22 (3)	.99
PLTC 0-4 hours, units (patients transfused)	42 (6)	22 (3)	.3
Total PLTC, units (patients transfused)	64 (6)	46 (4)	.3
Total number of patients transfused (%)	185 (36)	178 (34)	.5

FFP, Fresh frozen plasma; *OR,* operating room; *PLTC,* platelet concentrate; *PRBC,* packed red blood cells.
*χ^2 Test; no differences between groups.

most effective; it is the most widely studied, and it is the protocol used in our study. Introduced for the treatment of high-risk patients (those having repeat operations, endocarditis, or preoperative aspirin), it has also proven effective in low-risk patients.[11-14] Tranexamic acid is a synthetic antifibrinolytic drug more recently introduced in cardiac surgery. It acts by forming a reversible complex with the plasminogen through the lysine binding sites for fibrin. The saturation of these sites displaces the plasminogen from the fibrin surface, preventing the binding of plasmin to fibrinogen or to fibrin monomers.[15]

When we started our studies on antifibrinolytic drugs, few studies comparing high-dose aprotinin with tranexamic acid had been performed. The results were ambiguous and limited to small series of patients.[16-20] Before starting this trial, we performed a pilot prospective randomized study in which 210 patients received tranexamic acid, ε-aminocaproic acid, or aprotinin, evaluating postoperative bleeding and the need for allogeneic transfusions. The results were that tranexamic acid but not ε-aminocaproic acid showed effects similar to those of aprotinin.[21] Therefore, to confirm these initial results, we decided to compare aprotinin and tranexamic acid in a large number of patients scheduled for primary elective cardiac surgery. We did not consider a control group necessary because we deemed satisfactory the number of studies in the literature in which the efficacy of the 2 drugs had been demonstrated when compared with a placebo.[11-14,22,23]

A discussion of our results must consider the differences between the 2 groups as shown by statistical analysis. In line with previous reports, we found aPTTs to be significantly longer in the aprotinin group. This difference is due to the inhibition of the bean phosphatide activator used in the whole blood aPTT assay induced by aprotinin.[24] The other differences are likely due to the large size of the series we studied. The differences of postoperative data (minimum temperature during CPB and number of distal anastomoses performed) and postoperative values of hematocrit and hemoglobin are very small and without clinical significance; particularly in the aprotinin group, the hematocrit and hemoglobin values are only slightly higher at each point (eg, 1% and 0.4 g/dL, respectively, at time 4). The median of total blood

Table VII. *Postoperative outcomes and complications*

	Aprotinin group (N = 518)	*Tranexamic acid group (N = 522)*	P*
Intubation time, h	9 [7-11]	9 [7-11]	.5
ICU stay, days	1 [1-2]	1 [1-2]	.6
Hospital stay, days	9 [7-11]	9 [7-10]	.09
Re-exploration for bleeding without surgical source, No. (%)	3 (0.6)	3 (0.6)	.99
Re-exploration for surgical bleeding, No. (%)	5 (1)	7 (1.3)	.8
Excessive blood loss, No. (%)	51 (9.8)	53 (10.1)	.8
Perioperative AMI, No. (%)	9 (1.7)	11 (2.1)	.7
Early reoperation for ischemia, No. (%)	3 (0.6)	3 (0.6)	.99
Postoperative renal insufficiency:			
Creatine twice the baseline, No. (%)	17 (3.3)	16 (3.1)	.8
Postoperative dialysis, No. (%)	7 (1.4)	7 (1.3)	.8
Pulmonary embolism, No. (%)	0	1 (0.2)	.99
Major neurologic dysfunction, No. (%)	4 (0.8)	4 (0.8)	.99
Death, No. (%)	12 (2.3)	10 (1.9)	.6

AMI, Acute myocardial infarction; *ICU,* intensive care unit. Excessive bleeding is considered as greater than 600 mL in the first 24 hours.
*The χ^2 test or Fisher exact test and Mann-Whitney *U* test were used as appropriate. Plus-minus values are mean ± standard deviation; non-normally distributed data are indicated as median and (in brackets) 25th to 75th percentiles.

loss is just 50 mL lower, with a confidence interval ranging from 0 to 50 mL, the value we considered to be clinically acceptable for equivalence between the 2 drugs. Furthermore, we did not find differences in the number of perioperative allogeneic transfusions, percentage of patients receiving a transfusion, and prevalence of re-exploration for bleeding. These results are similar to those shown in a recent study.[25]

However, there are impressive differences regarding the cost of the 2 drugs: for our institution the high-dose aprotinin protocol costs an average of $370 per patient, whereas the described tranexamic acid protocol costs about $4 per patient. We annually perform about 1500 elective operations, and this results in a cost difference of about $500,000. To reduce the cost of treatment with aprotinin, various authors suggested the administration of lower doses; 2 regimens have been principally studied: half-dose or pump-prime only dosage. The results of these studies are not uniform, and the safety of these pharmacologic protocols is questionable.[26,27]

Another limit related to the use of aprotinin is the probability of anaphylactic reactions. Recent studies have shown the incidence of such reactions to be 1% to 2% for the first exposure and 2% to 4% at re-exposure.[6-28] This is an important concern because of the progressive increase in patients undergoing redo cardiac operations. In our study, only 1 patient with no history of allergy or previous administration of aprotinin had anaphylactic shock at the start of the initial bolus, which required emergency pharmacologic treatment and CPB support. The analysis of postoperative complications does not show any difference between the 2 groups and is in line with the data reported in the literature.

An important point about the safety of antifibrinolytic therapy concerns the risk of thrombosis, particularly of venous grafts. In our study, the 2 groups showed the same low incidence of perioperative myocardial infarction (about 2%). In a recent large multicenter study, 2928 grafts in 870 patients were analyzed by early angiography. No significance difference was observed between the 436 patients treated with aprotinin and the 434 treated with placebo in perioperative acute myocardial infarction and mortality; however, an increased probability of early occlusion of venous grafts in vessels less than 1.5 mm in diameter or of poor quality (aprotinin group 15.4% vs control group 10.9%; $P = .03$) was seen in patients treated with aprotinin.[29] Incomplete revascularization resulting from early graft occlusion may predispose the patient to late myocardial infarction, recurrent angina, and reduced event-free survival, suggesting caution regarding an indiscriminate use of aprotinin.[30]

Finally, in analyzing data about the intubation time, ICU and hospital stays, and incidence of mortality, we observed no differences between the groups, demonstrating that the different treatment does not affect the outcome.

Conclusions

Our study clearly demonstrates in a large population undergoing primary elective cardiac surgery that tranexamic acid is clinically as effective as high-dose aprotinin in preventing perioperative bleeding and the need for allogeneic transfusions. Because of the lower costs and a lower risk of adverse reactions, we think that tranexamic acid is preferable to aprotinin in this type of patient.

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Appendix

Reasons	*Aprotinin group (N = 518)*	*Tranexamic acid group (N = 522)*
Pharmacologic protocol error, No. (%)	0	1 (0.2)
Anaphylactic shock, No. (%)	1 (0.2)	0
Intraoperative surgical complications necessitating homologous transfusions, No. (%)	3 (0.6)	3 (0.6)
Delayed sternal closure for weaning from CPB, No. (%)	2 (0.4)	1 (0.2)
VAD for weaning from CPB, No. (%)	3 (0.6)	3 (0.6)
Re-exploration for surgical bleeding, No. (%)	5 (1)	7 (1.3)
Early reoperation for ischemia, No. (%)	3 (0.6)	3 (0.6)
Total number (%)	17 (3.4)	18 (3.5)

There were no significant differences between the 2 groups. *CPB,* Cardiopulmonary bypass; *VAD,* ventricular assist device.